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HEALTH RISKS OF PASSIVE SMOKING: PROBLEMS OF INTERPRETATION

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Introduction

It is notoriously difficult to draw sound conclusions about causation from epidemiologic studies of associations. In his *Principles of Medical Statistics*, Sir Austin Bradford Hill, one of the founders of modern epidemiology, warns in connexion with positive associations: "Merely to presume that the relationship is one of cause and effect is fatally easy; to secure satisfactory proof or disproof, if it be possible at all, is often a task of very great complexity" (Hill, 1949).

The fundamental difficulty in conventional case-control and prospective surveys relates to the comparability of cases and controls. Thus, when we compare the incidence of lung cancer in smokers with that in nonsmoking controls we determine an association which, in the great majority of studies (U.S. Surgeon General, 1982), has been found to be positive. But, as we have been told *ad nauseam*, "association does not necessarily imply causation." Smokers and nonsmokers are generally self-selected and we need to be assured of the strict comparability of the two groups—in every pertinent respect except smoking—before inferring causation from association (Fisher, 1959; Yerushalmy, 1971). An analogous issue arises in connexion with various studies of passive smoking (Burch, 1981a): are persons married to smokers comparable, on the average, in all other pertinent respects to persons married to nonsmokers? Alas, the phenomenon of assortative mating is well established and accordingly we are not at liberty to assume that studies of any disease, in relation to the smoking status of the spouse or other household members, comply with the scientific requirements for valid inferences about cause. The nonsmoker who marries a smoker is unlikely to be representative of all nonsmokers.

My main purpose here is to examine Repace and Lowrey's (1985) arguments about lung cancer from the methodologic viewpoint.

Outline of Repace and Lowrey's Procedure

1. Exposure of nonsmokers

From measurements of the concentration of respirable particles between 0.01 and 3.0 μm diameter in representative samples of room air, and from surveys of lifestyles, Repace and Lowrey (1985) estimate the total exposures of nonsmokers (range and average) in terms of mg cigarette tar per day.

2. Epidemiologic studies of lung cancer in passive smokers

They review 13 epidemiologic studies of lung cancer risk in the nonsmoking spouses of cigarette smokers. In 12 of these, the only index of exposure was the strength of the spouse's smoking habit. The mortality ratio for persons married to smoking spouses versus those married to nonsmokers, clusters around a value of 2.0.

They also compare the sex- and age-adjusted mortality from lung cancer in Seventh Day Adventists (SDA) self-reported nonsmokers with that in never-smokers in the general U.S. population. Non-SDA never-smokers had an average standardized death rate from lung cancer that was 2.4 times that of SDA never-smokers. This latter group, they believe, was less likely to be exposed to ambient tobacco smoke than the former.

3. Estimated death-rate from lung cancer in nonsmokers using epidemiologic studies of passive smoking

Repace and Lowrey (1985) assume that the mortality ratio (2.4) derived from the SDA study implies causation and thereby calculate that some 4,700 lung cancer deaths per year have been caused among U.S. nonsmokers owing to passive smoking. They conclude that this figure agrees well (within 10%) with

Hirayama's (1981) estimate of mortality from lung cancer attributable to passive smoking by the nonsmoking wives of Japanese smokers.

4. Estimated death-rate from lung cancer in nonsmokers using epidemiologic studies of active smokers

From many studies of lung cancer in active cigarette smokers reviewed by the U.S. Surgeon General (1982), and a linear exposure-response relationship, Repace and Lowrey derive an alternative estimate of the lung cancer death rate in the U.S. resulting from passive smoking. This procedure leads to an estimated 555 lung cancer deaths per year, nearly one order of magnitude lower than the rate (4700 per year) calculated under procedure 3 above.

5. Discussion of discrepancy between procedures 3 and 4

Repace and Lowrey speculate upon ways in which the lower estimate might be raised to the upper value.

Critique

Each of the above stages in Repace and Lowrey's procedure is discussed in turn.

1. Comment on: Exposure of nonsmokers

To make a valid estimate of the effective exposure of passive smokers to carcinogens we require the following information at least: (i) the nature of the carcinogens and their concentration in sidestream smoke particles; (ii) the anatomical location of the target cells; (iii) appropriate parameters of exposure such as the time-concentration and/or integral dose of carcinogens at the cells at risk; and (iv) an established model of tobacco smoke carcinogenesis incorporating factors for the sex- and age-dependence, dose and dose-rate effects, genetic susceptibility, etc..

Having little or no definitive guidance under any of these requirements, current estimates of effective exposure to carcinogens should be regarded as conjectural. Nevertheless, for the purpose of comparing passive smoking with active smoking, we have at present little option but to use the kind of data given in Repace and Lowrey's Table 1, although, according to Jarvis and Russell (1984), measurements of cotinine concentrations in urine samples are preferable.

2. Comment on: Epidemiologic studies of lung cancer in passive smokers

In addition to problems concerning occupational hazards, the choice of controls, etc., the reviewed epidemiologic studies are vulnerable to one elementary as well as a fundamental objection. To take the elementary objection first, Repace and Lowrey's Table 1 gives an estimated average daily exposure of nonsmokers in the home only, of 0.10 mg, and at work only, of 0.44 mg. It follows that studies of cancer and lung cancer risk in passive (or active) smokers, in relation to the smoking status of the spouse and household members, provide wholly inadequate evidence for association with actual exposure. Average total exposure appears from Repace and Lowrey's calculations to be dominated by the workplace component. This view is borne out in the Japanese environment by actual measurements of cotinine concentrations in urine samples from 167 male and 305 female nonsmokers (Matsukura *et al.*, 1984). Using Duncan's multiple-range test for several comparisons the authors found no significant difference between persons (200) not exposed at home, who had an average concentration of 0.51 $\pm$0.09 μg/mg creatinine, and those (272) exposed at home who had an average of 0.79 $\pm$0.10 μg/mg creatinine. Consequently, the relatively large differences in cancer risk between persons with smoking spouses, and those with nonsmoking spouses, are most unlikely to be due to differences in the levels of passive smoking, which on the average are small.

Only one study, that of Kabat and Wynder (1984), took account of exposure of nonsmokers in the workplace. That survey disclosed 6 male cases and 5 controls exposed in the home but 18 (out of 25) cases and 11 (out of 25) controls exposed at work ($P = 0.05$, ignoring the problem of multiple tests). With respect to women, Kabat and Wynder (1984) report: ". . . 16 of 53 cases were exposed at home compared to 17 of 53 controls, and 26 of 53 cases were exposed at work compared to 31 of 53 controls." Thus no significant differences were found in the data for women but the trend favours a prophylactic rather than a causal hypothesis.

The fundamental objection to all the reviewed studies of passive smoking concerns, of course, the lack of established comparability between the exposed and the nonexposed groups. This objection applies equally to studies of cancer risk in relation to the spouse's and household smoking, and to the comparison between SDA and non-SDA never-smokers. Seventh Day Adventists differ from never-smokers in the general U.S. population with respect to various features of lifestyle. Moreover, they are not drawn randomly from the general population; they are either self-selected and/or born of self-selected parents.

Hence, no reliable inferences about cause can be drawn from associations determined from either of the above types of evidence. In the absence of randomization we can have no confidence that hidden variables, particularly of a constitutional character, are not responsible for the observed associations.

By an interesting irony one of the studies of passive smoking (Sandler, *et al.*, 1985a, 1985b), if taken at face value, provides a fair refutation of the hypothesis

that the association with the risk of cancer is causal (Burch, 1985). Sandler *et al.* (1985a) studied the overall cancer risk in active and nonsmokers in relation to the number of household members who smoke. The odds ratio was normalized to unity for households with no (other) members who smoked. For households with one (other) smoking member the odds ratios are 1.42 for active smokers and 1.45 for nonsmokers; for households with two (other) smokers the corresponding ratios are 2.25 and 2.32; and for three or more, the ratios are 2.42 and 2.75. Within the error limits the ratios for active smokers are identical with those for nonsmokers. Treating them as identical, Burch demonstrated that if A represents the carcinogenic effect of active smoking and P the carcinogenic effect of passive smoking resulting from one household smoker then, for either additive or multiplicative (interactive) models of carcinogenesis, $A + P = 0$ (Burch, 1985). This relation has three possible solutions: (i) active and passive smoking are both noncarcinogenic ($A = P = 0$); (ii) active smoking is carcinogenic and passive smoking is prophylactic ($A = -P$); and (iii) active smoking is prophylactic and passive smoking is carcinogenic ($P = -A$). Burch added: "The statistical uncertainty in Sandler's Table 1 is large enough to permit slightly less paradoxical inferences . . ."

Sandler *et al.* (1985b) replied to this analysis giving a further breakdown of their data showing odds ratios for the overall cancer risk in active and in nonsmokers in relation to household exposure to cigarette smoke during childhood only, adulthood only, and both periods of life. These supplementary data only deepen the paradox: Consider the simple additive model and define N as the average risk per person of cancer from all causes unconnected with smoking; A is the average additional risk from active smoking, including the smoker's exposure to the associated ambient cigarette smoke; P_c is the additional average risk from exposure to household cigarette smoke during childhood only; and P_A is the corresponding risk from exposure to household cigarette smoke during adulthood only. (The study population was aged from 15 to 59 yr and I assume these risks are substantially less than unity.) For nonsmokers exposed to household cigarette smoke during childhood only, with total risk $N + P_c$, we require from the Table of Sandler *et al.* (1985b): $(N + P_c)/N \cong$ the odds ratio, 1.3, giving $P_c \cong 0.3N$, a nonparadoxical result. For active smokers who were exposed to household cigarette smoke during childhood only, we have: $(N + A + P_c)/(N + A) \cong 1.9$. Substituting for P_c, we obtain $A \cong -0.7N$, a highly paradoxical result implying that active smoking in conjunction with passive exposure to household cigarette smoke during childhood only, is markedly prophylactic! A similar conclusion emerges from the multiplicative model.

However, when we consider the odds ratios for exposure to household cigarette smoke during adulthood only, we obtain $A \cong 3N$, which for the overall cancer risk in both sexes is substantially larger than directly observed associations (U.S. Surgeon General, 1982). Furthermore, although it is logically acceptable that active smoking in conjunction with passive smoking during childhood only is prophylactic, but in conjunction with passive smoking during adulthood only it is carcinogenic, the sharp reversal of effect between childhood and adult phases imposes a severe strain on biological models of carcinogenesis.

The "solution" to these findings of Sandler *et al.* (1985a, 1985b) that minimises paradox is, in effect, the original one: $A = P_c = P_A = 0$; with the odds ratios being attributed to selection effects arising from assortative mating.

3. Comment on: Estimated death-rate from lung cancer in nonsmokers using epidemiologic studies of passive smoking

Even if we adopt the hypothesis that passive smoking causes lung cancer and ignore selection problems, the evaluation of the epidemiologic studies for the purpose of risk calculations still poses severe problems. We have no direct measure of the relevant exposure to ambient cigarette smoke in any of the studies of associations. Although it is plausible to suppose that SDA nonsmokers have a lower exposure to ambient cigarette smoke than non-SDA never-smokers, we have no direct measure of the average levels in either group.

For these reasons alone the calculation by Repace and Lowrey of the number of lung cancer deaths (LCDs) per year in the United States caused by passive smoking must be regarded with the utmost suspicion. Associations determined from conventional case-control or prospective nonrandomized surveys should play no part in a scientific estimate of the magnitude of risks.

4. Comment on: Estimated death-rates from lung cancer in nonsmokers using epidemiologic studies

From the Surgeon General's estimate that 85% of all lung cancers are due to smoking and a linear exposure-response relation, Repace and Lowrey calculate that about 555 LCDs are caused in the United States each year through nonsmokers being exposed to ambient tobacco smoke. Elsewhere I have reviewed the methods used in the U.S. Surgeon General's (1982) report on cancer and, in particular, the arguments about lung cancer (Burch, 1983). If Lilienfeld's (1983) invited response to my many criticisms may be regarded as the best available defence of the Surgeon General's methods then I hope that I might be forgiven for suggesting that we need give little credence to them (Burch, 1984).

To quote from my summary (Burch 1983): "Part II of the [Surgeon General's] Report describes the five criteria for causality that have guided the judgment of committees since 1964. I show that not one of the criteria, plausibly interpreted, is satisfied by the epidemiologic evidence for lung cancer." Lilienfeld (1983) was unable to demonstrate the contrary and to all my pointed enquiries he did not supply a single answer. On the Surgeon General's own criteria the hypothesis that the association between smoking and lung cancer is entirely causal in origin should be rejected.

My main attack, however, was launched at a more fundamental level: "The five criteria and the subjective method of 'judgment' are inappropriate to a scientific analysis; they should be replaced by the objective testing of hypotheses." Given a genuine association between a habit, *H*, such as cigarette smoking, and a cancer, *C*, such as lung cancer, we are obliged to consider all the following possibilities: (i) *H*, or something closely connected with it, such as the means of ignition, causes *C*; (ii) *C*, or a connected pre-*C* condition, causes *H* (I call this the "converse causal" hypothesis); (iii) a "third" factor causes, or predisposes to, both *H* and *C*; and (iv) because (i) to (iii) are not mutually exclusive any combination of them might be needed to account for an established association.

A comprehensive evaluation of an association requires an assessment of the relative contributions of (i), (ii) and (iii) complete with confidence limits. I had to admit: "My own attempts to derive the magnitude of the causal component of the association between smoking and lung cancer have been unsuccessful; errors of diagnosis and death-certification alone are apt to defeat such efforts." We are fortunate that other investigations—see below—help us to arrive at a "best estimate" of this causal component.

5. Comment on: Discussion of discrepancy between procedures 3 and 4

On encountering a near order of magnitude discrepancy between alternative estimates, most investigators would express dismay; it is to the credit of Repace and Lowrey that they display no outward signs of disappointment. Nevertheless, their ". . . discussion of alternative exposure-response relationships" has one conspicuous feature. Means are sought only to raise the lower estimate of 555 LCDs per year to the higher (4700 LCDs per year) and none in the reverse direction. I suggest that as little faith should be vested in the one estimate as in the other; both incorporate the same fundamental fallacy of arguing from association to causation.

It is widely, one hopes universally, recognized that the best way of eliminating most forms of bias, both in therapeutic trials and in epidemiologic studies of causation, is through randomization. Feinstein (1985) describes the randomized trial as the definitive "gold" standard in epidemiology. In the only practical form of such trials so far exploited in connection with the effects of active smoking, persons satisfying defined entry criteria were allocated randomly to one of two groups: (a) the intervention group which was subjected to intensive advice on the part of the investigators to quit smoking; or (b) the usual care, control group, which received no such advice. Levels of smoking were then monitored in both groups and after a suitable period the outcome, mainly in terms of mortality from various diseases and all causes, was assessed for the two groups.

Two such randomized trials have been carried out in which the findings for lung cancer have been reported: the Whitehall Study in London, England (Rose *et al.*, 1982) with a 10-yr follow-up; and the Multiple Risk Factor Intervention Trial (MRFIT, 1982) in the United States with a 7-yr follow-up. Although this latter trial cost some $120 million and, aiming at a reduction of heart disease, included dietary advice and stepped care treatment for hypertension in the intervention group—as well as antismoking advice—the results have not achieved prominence in the medical literature. They are not even mentioned by Repace and Lowrey. It is remarkable that reputable trials that cost so much should be valued so little.

Substantial reductions in smoking were achieved through the efforts of the investigators in the intervention groups, over and above the unplanned reductions in the usual care, control groups. By combining deaths and registrations for lung cancer in the Whitehall Study with deaths from lung cancer in the MRFIT (registrations not being reported in that study) we maximize numbers and obtain the best available direct epidemiologic test of the efficacy of reducing or quitting cigarette smoking. In the combined intervention, low-smoking groups, some 56 cases of lung cancer were recorded out of 7,142 men at entry (0.78%); in the usual care, relatively high-smoking groups, 53 cases were found out of 7,169 at entry (0.74%). The small advantage enjoyed by the high-smoking groups is, of course, not statistically significant; but it is strikingly consistent with the hypothesis that the association of active smoking with lung cancer has little or no causal component.

Because Sandler *et al.* (1985a, 1985b) studied all types of cancer, the outcome of the randomized trials for all cancers other than lung cancer are also of special interest. Some 88 cases (1.23%) were recorded in the combined low-smoking intervention groups but only 60 cases (0.84%) in the more heavily smoking usual care groups! It would be interesting to know whether a detailed statistical analysis of these combined results would reject the null hypothesis, as it did in the Whitehall Study at the level $P = 0.003$ (Rose *et al.*, 1982).

One possible weakness of this type of intervention trial must be mentioned. Quitting smoking might be followed by psychological stress, or other changes in lifestyle, that are carcinogenic. Rose *et al.* (1982) observed only "minor" psychological effects of intervention but believe that further study is needed to test the hypothesis that quitting smoking has adverse effects on the cancer risk.

Before concluding the review of these randomized trials the findings for deaths from all causes should be quoted because they yield the largest numbers and have some claim to be the most important. In the combined intervention groups, 388 deaths in 7,142 were reported (5.43%); and in the more heavily smoking control groups, 388 deaths in 7,169, or 5.41%, were reported. (It should be remembered that in the MRFIT study the intervention group also received dietary advice and treatment for hypertension.) Suffice it to say that a reduction in overall mortality does not appear to be among the benefits of quitting smoking.

This is not an isolated finding; it corroborates an earlier analysis (Burch, 1981b) that was also designed to defeat the bias of self-selection and was exempt from the problems connected with intensive intervention. To avoid the errors of certification of the cause of death I analysed the temporal trends in sex- and age-specific mortality from all causes in England and Wales, over the period 1950 to 1976. These trends were compared, for various latent periods, with the corresponding temporal trends in sex- and age-specific rates of cigarette consumption (on a "constant tar" basis), which rose during the early part of the period surveyed and fell during the latter part. The fall in death rates was greater during the rise in cigarette consumption than during its fall. Differences in the age-pattern of mortality between the early and late periods showed that, up to the age of about 45 yr, the fall in overall mortality was almost entirely accounted for by the near eradication of tuberculosis. No causal effects of smoking on overall mortality could be discerned although, if the associations observed in case-control and prospective studies had a causal basis, they should have been readily detected.

Conclusions

When the most reputable of direct epidemiologic studies, randomized controlled intervention trials, fail to demonstrate any of the benefits widely expected from quitting active smoking, it is not surprising that Repace and Lowrey's alternative estimates of the effects of passive smoking on the incidence of lung cancer—both based on spurious arguments—should differ by almost an order of magnitude. The conclusion that exposure to ambient tobacco smoke produces ". . . about 5000 lung cancer deaths per year in U.S. nonsmokers aged > 35 years . . ." belongs more to speculation than reality. When we take into account the outcome of the randomized trials together with the paradoxical implications of the findings of Sandler *et al.* (1985a, 1985b), the best estimate of LCDs per year is approximately zero.

No methodologically sound investigation of putative carcinogenic effects of passive smoking has yet been carried out. In the light of the size and cost of the randomized trials of the effects of quitting smoking—and of the disappointing results—it must be doubted whether any methodologically sound study of the requisite sensitivity will be undertaken in connexion with passive smoking in the foreseeable future.

Repace and Lowrey may feel justified in—and can hardly be blamed for—following practices that, in spite of numerous warnings (Hill, 1949; Fisher, 1959; Brownlee, 1965; Yerushalmy, 1971; Feinstein, 1979) are still commonplace in epidemiology. In the words of a distinguished clinical epidemiologist, a "licensed" epidemiologist ". . . can obtain and manipulate the data in diverse ways that are sanctioned not by the delineated standards of science, but by the traditional practice of epidemiologists" (Feinstein, 1979). We must hope that, before further public alarm is generated, wiser and more scientific counsels will prevail.

References

Brownlee, K. A. (1965) A review of "Smoking and Health." *J. Am. Stat. Assoc.* **60**, 722–739.

Burch, P. R. J. (1981a) Passive smoking and lung cancer. *Brit. Med. J.* **282**, 1393.

Burch, P. R. J. (1981b) Smoking and mortality in England and Wales, 1950 to 1976. *J. Chron. Dis.* **34**, 87–103.

Burch, P. R. J. (1983) The Surgeon General's "Epidemiologic criteria for causality." A critique. *J. Chron. Dis.* **36**, 821–836.

Burch, P. R. J. (1984) The Surgeon General's "Epidemiologic criteria for causality." Reply to Lilienfeld. *J. Chron. Dis.* **37**, 148–156.

Burch, P. R. J. (1985) Lifetime passive smoking and cancer risk. *Lancet* **1**, 866.

Feinstein, A. R. (1979) Methodologic problems and standards in case-control research. *J. Chron. Dis.* **32**, 35–41.

Feinstein, A. R. (1985) Experimental requirements and scientific principles in case-control studies. *J. Chron. Dis.* **38**, 127–133.

Fisher, R. A. (1959) *Smoking. The Cancer Controversy*. Oliver & Boyd, Edinburgh, Scotland.

Hill, A. B. (1949) *Principles of Medical Statistics*. Lancet Ltd., London.

Hirayama, T. (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. *Brit. Med. J.* **282**, 183–185.

Jarvis, M. J. and Russell, M. A. H. (1984) Measurement and estimate of smoke dosage to non-smokers from environmental tobacco smoke. *Europ. J. Resp. Dis.* **65**, Suppl 133, 68–75.

Kabat, G. C. and Wynder, E. L. (1984) Lung cancer in nonsmokers. *Cancer*, **53**, 1214–1221.

Lilienfeld, A. M. (1983) The Surgeon General's "Epidemiologic criteria for causality": A criticism of Burch's critique. *J. Chron. Dis.* **36**, 837–845.

Matsukara, S., Taminato, T., Kitano, N., Seino, Y., Hamada, H., Uchihashi, M., Nakajima, H. and Hirata, Y. (1984) Effects of environmental tobacco smoke on urinary cotinine excretion in nonsmokers. *New Engl. J. Med.* **311**, 828–832.

MRFIT Research Group (1982) Multiple risk factor intervention trial: Risk factor changes and mortality results. *J. Am. Med. Assoc.* **248**, 1465–1477.

Repace, J. L. and Lowrey, A. H. (1985) A quantitative estimate of

nonsmokers' lung cancer risk from passive smoking, *Environ. Int.* 11, 3–22.

Rose, G., Hamilton, P. J. S., Colwell, L. and Shipley, M. J. (1982) A randomized controlled trial of anti-smoking advice: 10-year results, *J. Epidemiol. Commun. Health* 36, 102–108.

Sandler, D. P., Wilcox, A. J. and Everson, R. B. (1985a) Cumulative effects of lifetime passive smoking on cancer risk, *Lancet* 1, 312–315.

Sandler, D. P., Wilcox, A. J. and Everson, R. B. (1985b) Lifetime passive smoking and cancer risk, *Lancet* 1, 866–867.

U.S. Surgeon General (1982) The health consequences of smoking. Cancer. U.S. Department of Health and Human Services, Washington, DC.

Yerushalmy, J. (1971) Self-selection—A major problem in observational studies, in *Proc. 6th Berkeley Symp. on Mathematical Statistics and Probability*, vol. IV: *Biology and Health*, L. M. Le Cam, J. Neyman, and E. L. Scott, eds., pp. 329–342. University of California Press, Berkeley, CA.